A Simple Procedure for Estimating Method Quantitation Limits

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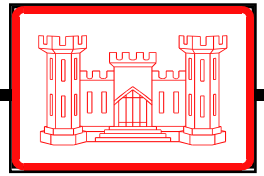
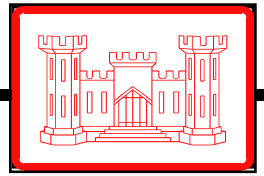


Overview of Topics

- Introduction
- Concepts and Procedures
- Examples
- QA/QC Issues
- Conclusions



Definition

Method Quantitation Limit (MQL) is the lowest amount of an analyte in a sample that can be quantitatively determined with stated, acceptable precision and accuracy under stated analytical conditions.

- **International Conference on Harmonization (ICH) Harmonised Tripartite Guideline**

Common Procedures

- Professional judgment
- Multiples of detection limit
- Lowest calibration standard
- Empirical procedures
- Lowest Concentration Minimum Reporting Level (LCMRL)

Professional Judgment

- Based on historical PQLs
- Based on EPA PE study data
- Based on arbitrary RSD
- Questionable data quality

Multiples of Detection Limits

- LOQ = 10 x SD = 3.3 x LOD
- MQL = 5 ~ 10 x MDL, but never < 3 x MDL
- Arbitrarily defined or determined
- Questionable precision and bias

Lowest Calibration Standard

- MQL = Lowest calibration standard
- Sample preparation not taken into account
- MQL depends on calibration techniques
- Questionable precision and bias

Empirical Determination

- Repetitive measurements at concentrations close to MQL
- MQL is determined based on the minimum concentration giving acceptable precision and bias
- Lacking standard procedures
- Expensive

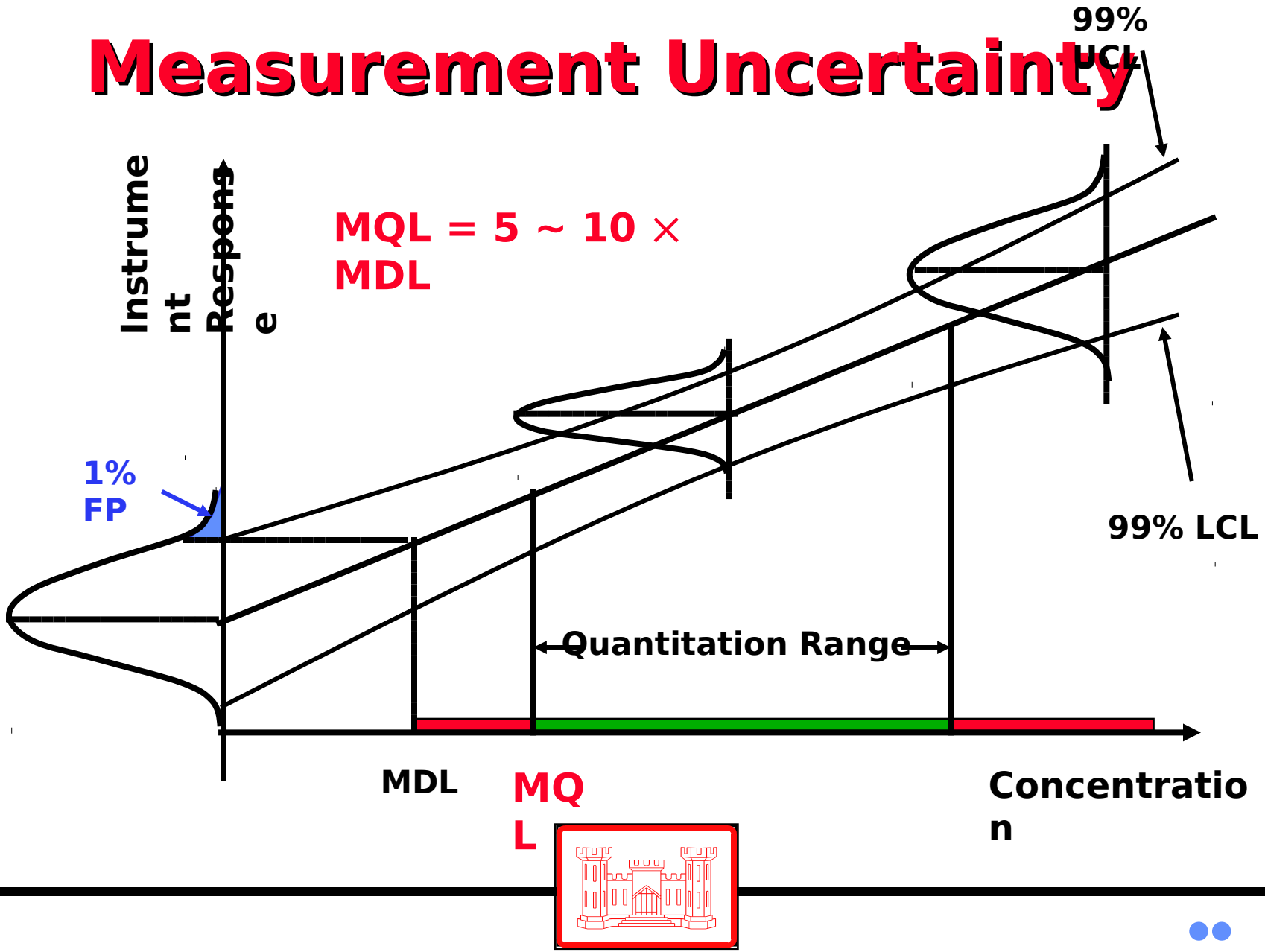
LCMRL (Lowest Concentration Minimum Reporting Level)

- EPA procedure for single-laboratory LCMRL and MRL (PQL) of UCMR
- Lowest concentration that future recovery will fall within specified recovery range and confidence
- Based on linear regression and prediction intervals for next observation
- Complicated and expensive

Concepts of Proposed Procedure

- Estimate MQL based on precision versus concentration
- Estimate precision based on routine QC data of MDL/MB and LCS
- Verify MQL on a routine basis

Measurement Uncertainty



Two-Component Model for Measurement Uncertainty

Rocke-Lorenzato Model

$$C = \varepsilon + \mu e^{\eta}$$

C measured concentration

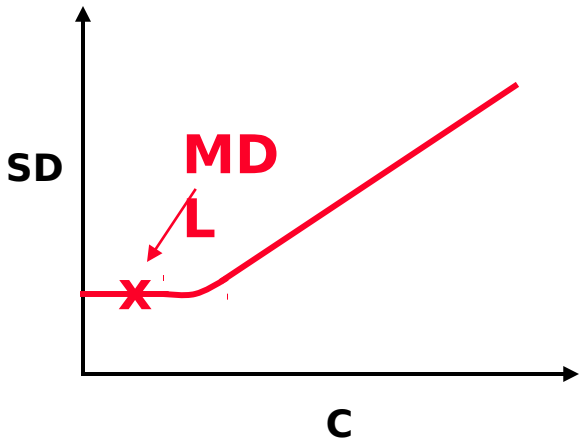
μ true concentration

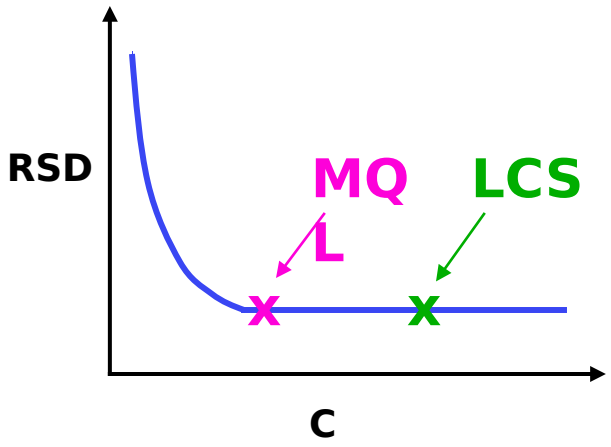
ε, η normally distributed uncertainty with mean 0 and standard deviation $\sigma_\varepsilon, \sigma_\eta$

Two-Component Model for Measurement Uncertainty

Rocke-Lorenzato Model

$$\sigma_C = \sqrt{\sigma_\varepsilon^2 + \mu^2 e^{\sigma_\eta^2}\left(e^{\sigma_\eta^2} - 1\right)}$$





Estimated Uncertainty at C < MQL

$U_{95\%}$ Relative uncertainty at 95% confidence

$$U_{95\%} = \pm \frac{t_{(n-1,.975)} \times \sigma_C}{C} \times 100\%$$

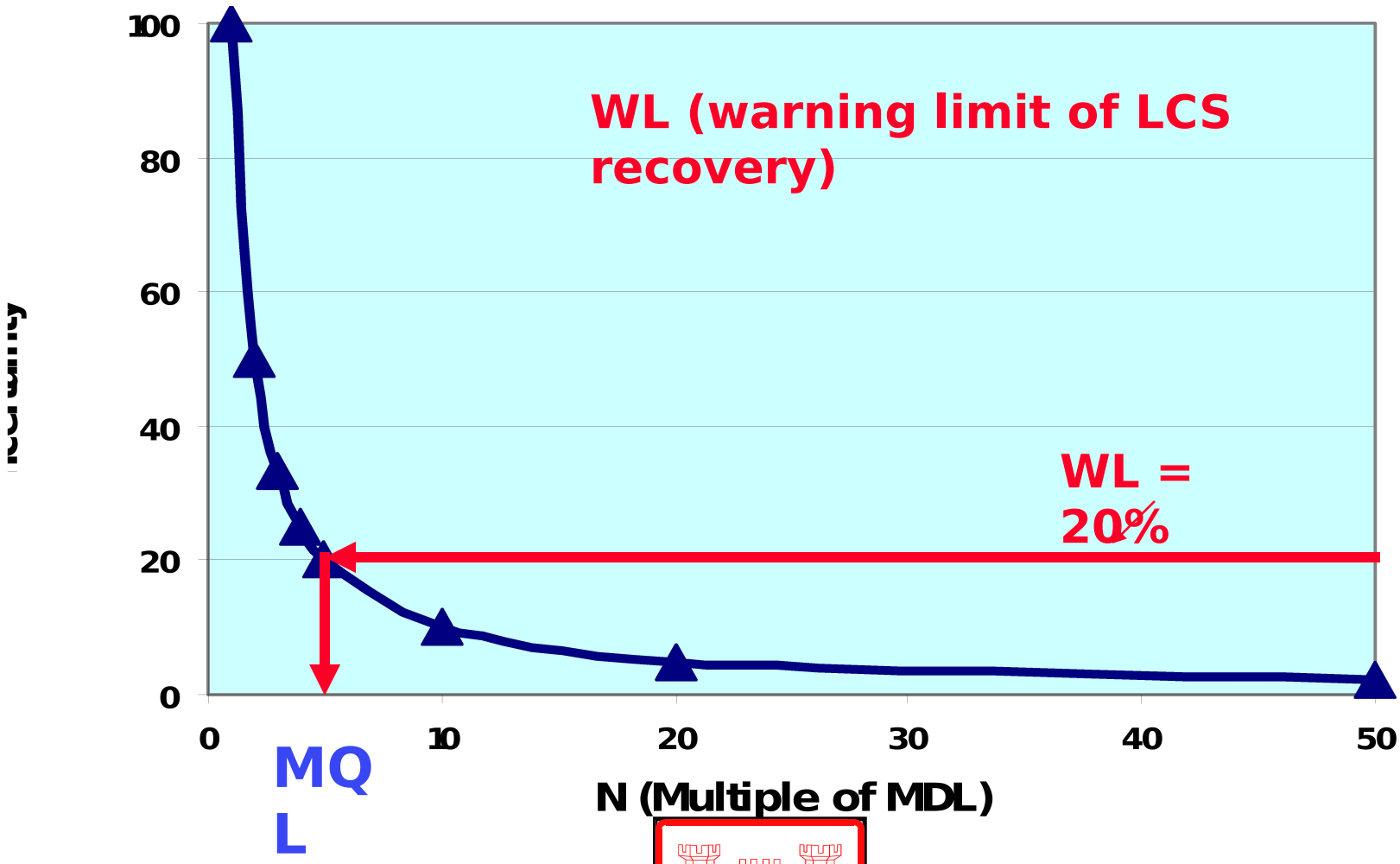
$$= \pm \frac{t_{(n-1,.975)} \times \sqrt{\sigma_\varepsilon^2 + \mu^2 e^{\sigma_\eta^2}(e^{\sigma_\eta^2} - 1)}}{C} \times 100\%$$

$$\approx \pm \frac{t_{(n-1,.975)} \times \sqrt{2} \times \sigma_\varepsilon}{N \times MDL} \times 100\%$$

$$= \pm \frac{t_{(n-1,.975)} \times \sqrt{2} \times \sigma_\varepsilon}{t_{(n-1,.99)} \times \sigma_\varepsilon} \times \frac{100\%}{N} \approx \pm \frac{100\%}{N}$$

$for C\ near MDL and C = N \times MDL.$

$U_{95\%}$ vs. Concentration



Proposed MQL Determination

MQL is established at the lowest concentration where $\boldsymbol{U_{95\%,\,MDL} = WL_{LCS}}$

$$\frac{100\%}{N} = WL_{LCS} = \frac{t_{(n-1,.975)} \times \sigma_{LCS}}{\overline{C}_{LCS}} \approx 2 \times RSD_{LCS}\%$$

$$N = \frac{100}{WL_{LCS}} \approx \frac{100}{2 \times RSD_{LCS}}$$

MQL = N x MDL

Example

MDL = 1 ppb, CL_{LCS} = 60 – 120%, MQL = ?

$$WL_{LCS} = \pm 20\%$$

$$MQL = N \times MDL$$

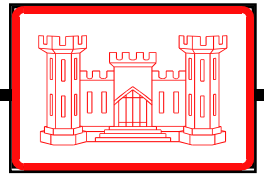
$$= \frac{100}{WL_{LCS}} \times MDL$$

$$= \frac{100}{20} \times 1 = 5\ ppb$$

with RSD = 10% and %R = 90%

Two-Component Model for Measurement Uncertainty

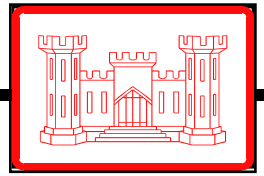
Analyte	Method	Spike Level	Mean Conc.	Mean (% Recovery)	SD Conc.	RSD (based on Mean)
1112-PCA	524.2	0.035				
1112-PCA	524.2	0.05				
1112-PCA	524.2	0.075				
1112-PCA	524.2	0.1				
1112-PCA	524.2	0.15	0.032	21.178	0.023	72.898
1112-PCA	524.2	0.2	0.090	44.886	0.020	22.297
1112-PCA	524.2	0.35	0.253	72.367	0.019	7.417
1112-PCA	524.2	0.5	0.416	83.143	0.013	3.211
1112-PCA	524.2	0.75	0.660	88.000	0.012	1.797
1112-PCA	524.2	1	0.830	82.986	0.035	4.185
1112-PCA	524.2	2	1.760	88.000	0.062	3.533
1112-PCA	524.2	5	4.239	84.771	0.132	3.104
1112-PCA	524.2	10	8.800	88.000	0.234	2.661
1112-PCA	524.2	20	16.729	83.643	0.486	2.902
1112-PCA	524.2	50	43.957	87.914	0.846	1.925
1112-PCA	524.2	100	94.543	94.543	2.625	2.776
1112-PCA	524.2	200	235.429	117.714	9.253	3.930



MDL = 0.05

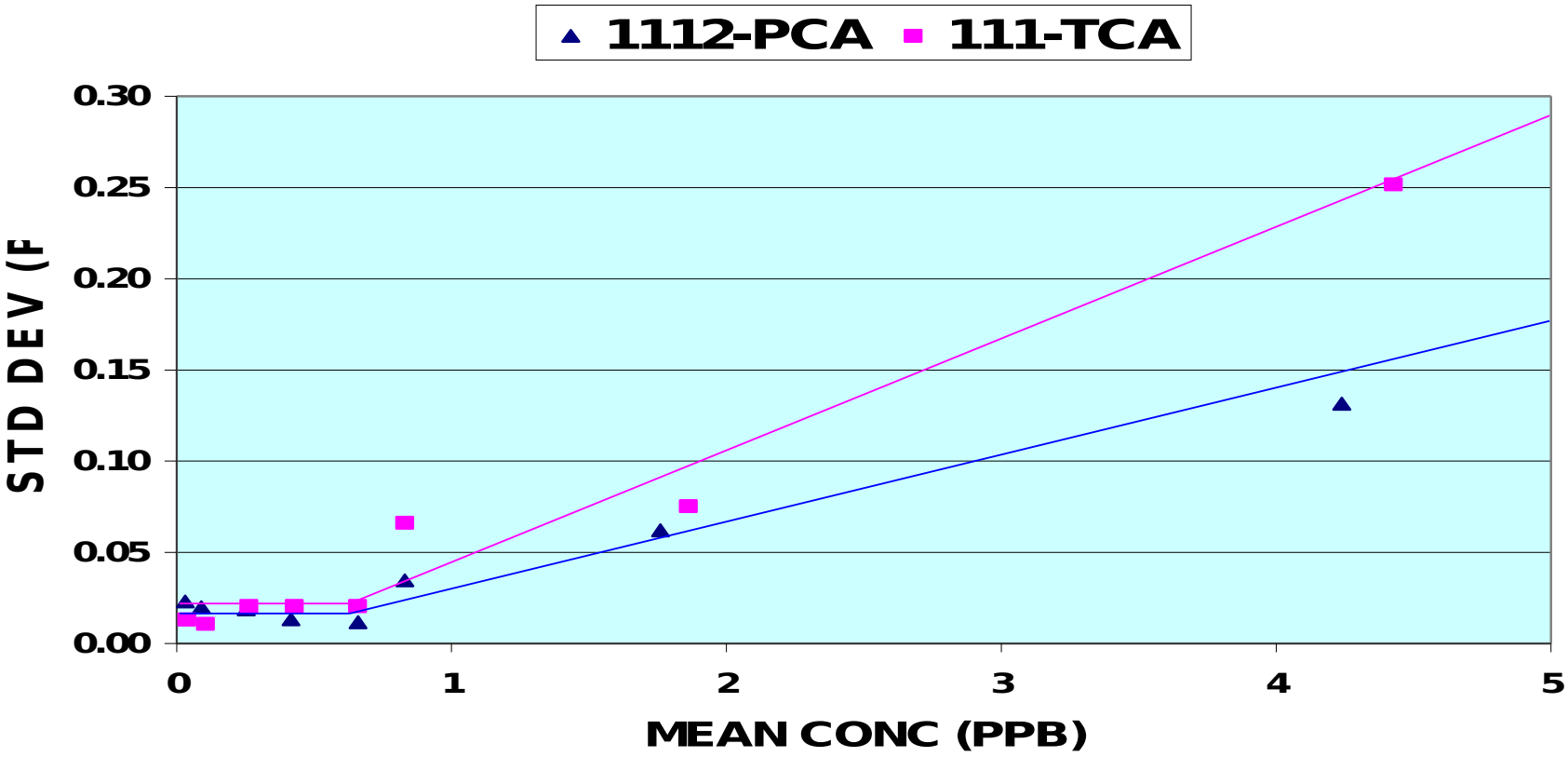
Two-Component Model for Measurement Uncertainty

Analyte	Method	Spike Level	Mean Conc.	Mean (% Recovery)	SD Conc.	RSD (based on Mean)
111-TCA	524.2	0.035				
111-TCA	524.2	0.05				
111-TCA	524.2	0.075				
111-TCA	524.2	0.1	0.146	146.000		
111-TCA	524.2	0.15	0.036	24.133	0.013	36.624
111-TCA	524.2	0.2	0.105	52.250	0.011	10.410
111-TCA	524.2	0.35	0.262	74.980	0.021	7.864
111-TCA	524.2	0.5	0.428	85.629	0.021	4.822
111-TCA	524.2	0.75	0.658	87.714	0.021	3.137
111-TCA	524.2	1	0.829	82.886	0.066	7.992
111-TCA	524.2	2	1.861	93.071	0.075	4.049
111-TCA	524.2	5	4.426	88.514	0.252	5.688
111-TCA	524.2	10	9.265	92.650	0.300	3.236
111-TCA	524.2	20	17.614	88.071	0.847	4.811
111-TCA	524.2	50	46.686	93.371	1.468	3.144
111-TCA	524.2	100	98.729	98.729	4.436	4.494
111-TCA	524.2	200	220.857	110.429	11.276	5.105

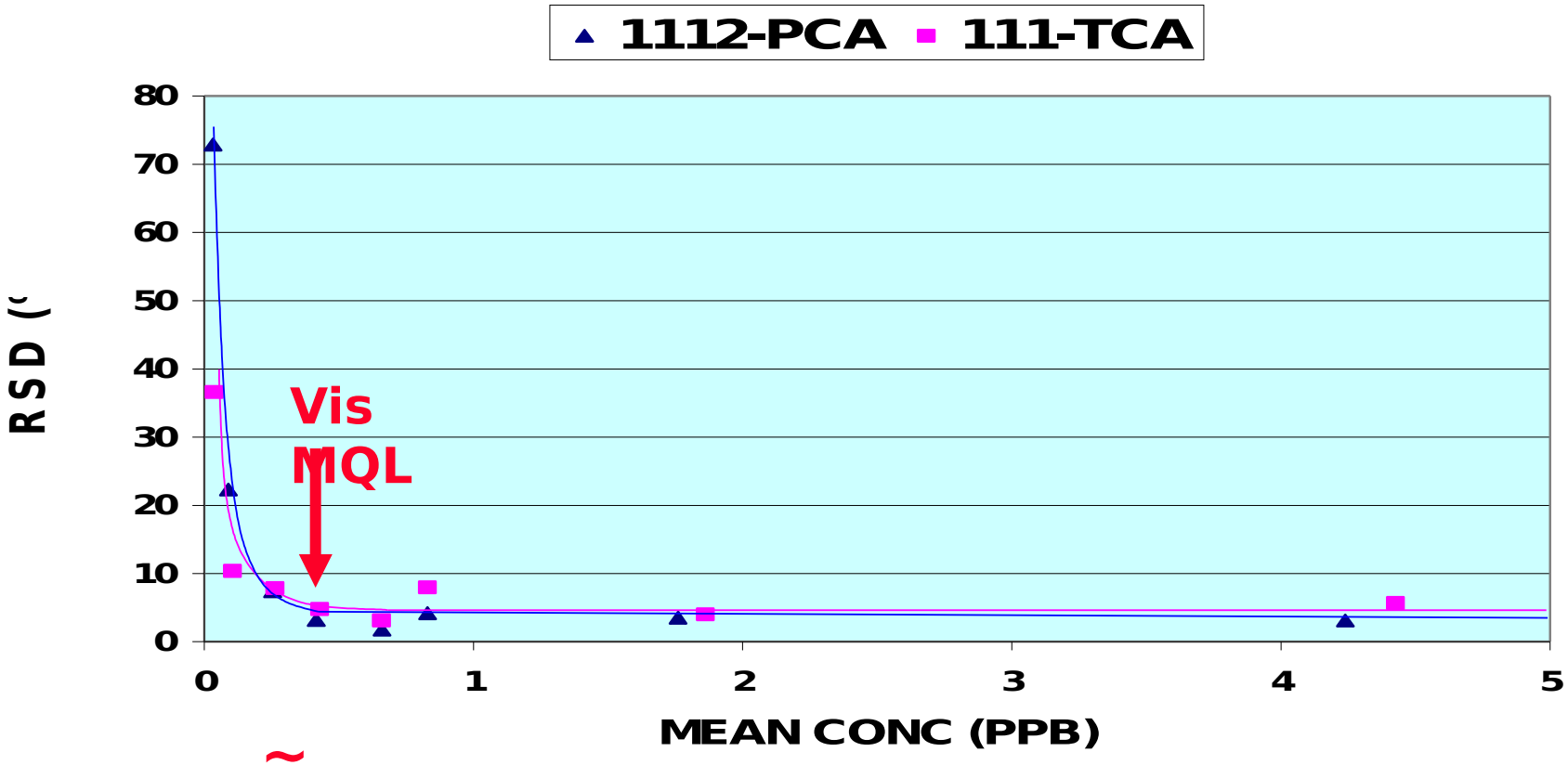


MDL = 0.06

Two-Component Model for Measurement Uncertainty



Two-Component Model for Measurement Uncertainty



~ 0.5

Example: 1112-PCA

MDL = t x σ = 3.143 x 0.017 = 0.05 ppb

MQL = 3 x MDL = 0.15 ppb

MQL = 5 x MDL = 0.25 ppb

MQL = 10 x MDL = 0.50 ppb

Which one is a reliable MQL?

Unknown: RSD_{LCS} = 3.0% ⇒ 2 x RSD_{LCS} = 6.0%

MQL = (100/6) x MDL = 0.83 ppb

with RSD = 3% and %R = 91%

Example: 111-TCA

MDL = t x σ = 3.143 x 0.018 = 0.06 ppb

MQL = 3 x MDL = 0.18 ppb

MQL = 5 x MDL = 0.30 ppb

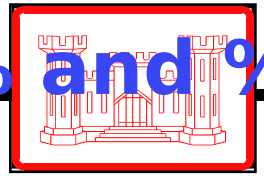
MQL = 10 x MDL = 0.60 ppb

Which one is a reliable MQL?

Unknown: RSD_{LCS} = 5% ⇒ 2 x RSD_{LCS} = 10%

MQL = (100/10) x MDL = 0.60 ppb

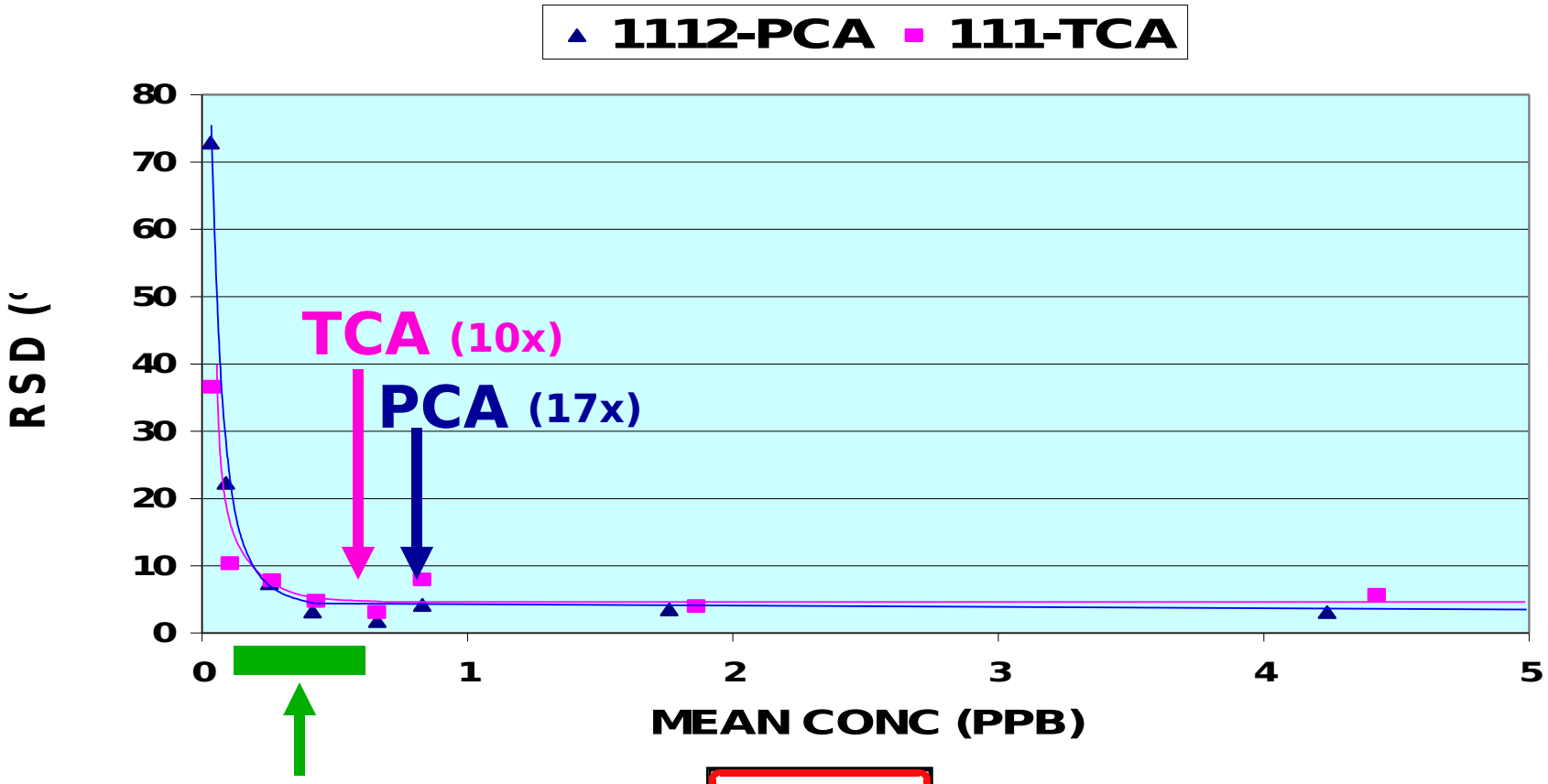
with RSD = 5% and %R = 93%



Comparison of MQLs

	PCA	TCA
MDL	0.05	0.06
CL_{LCS}	± 9%	±
15%		
3 x MDL	0.15	0.18
5 x MDL	0.25	0.30
10 x MDL	0.50	0.60
EPA ML	0.2	0.2
ISO LOQ	0.18	0.10
Calc MQL	0.83	0.60
(RSD/%R)	(3%/91%)	
(5%/93%)		

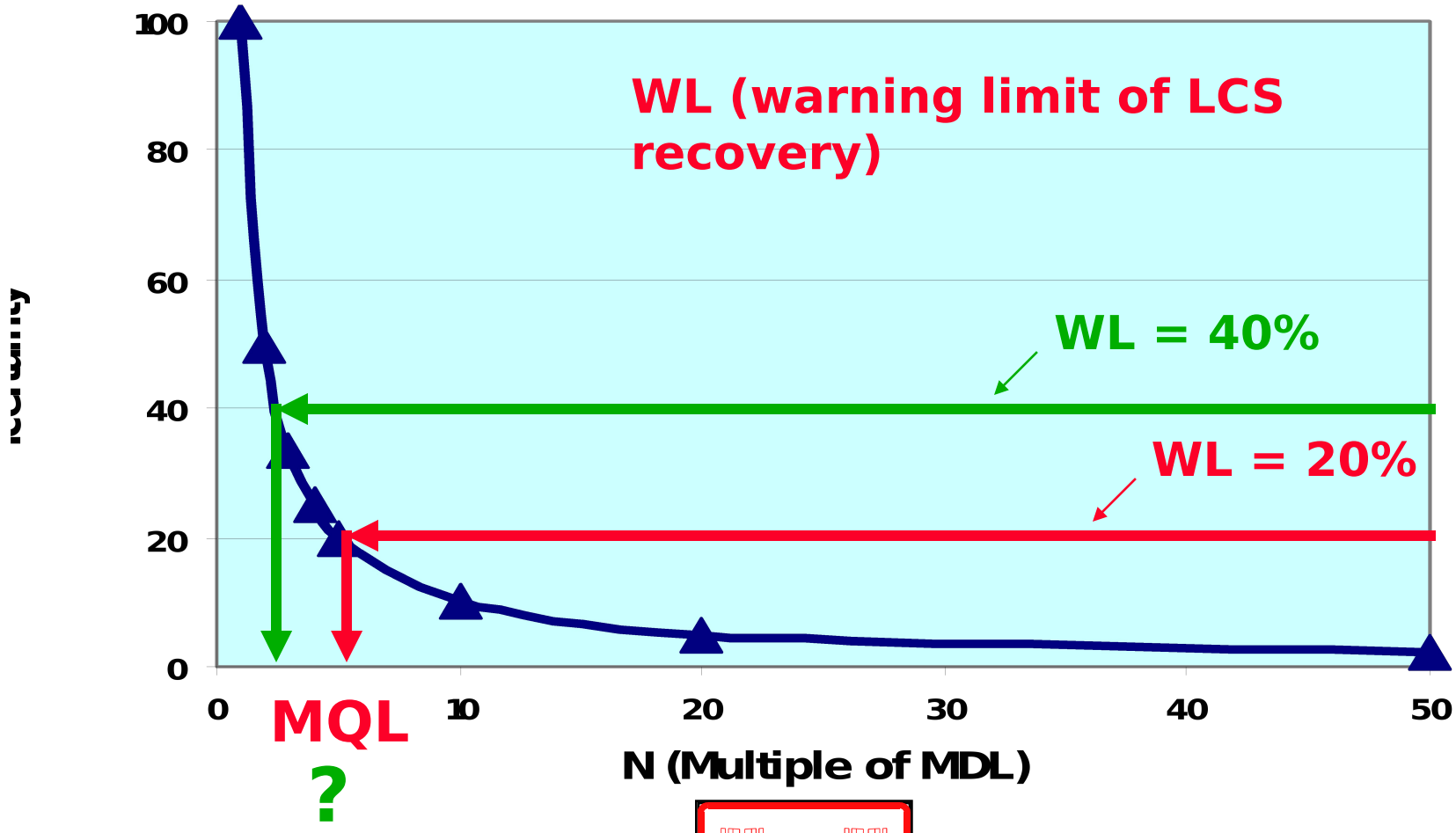
Two-Component Model for Measurement Uncertainty



MQL Calculator

ANALYTE	4-Nitrophenol	4-Nitrophenol
MATRIX	water	water
METHODS	3520C/8270C	3510C/8270C
MDL (ppb)	10	10
LCS LCL (%)	70	40
LCS UCL (%)	130	160
MQL (ppb)	50	25
PRECISION (RSD)	10	20
BIAS (%R)	100	100

MQL vs. RSD_{LCS}

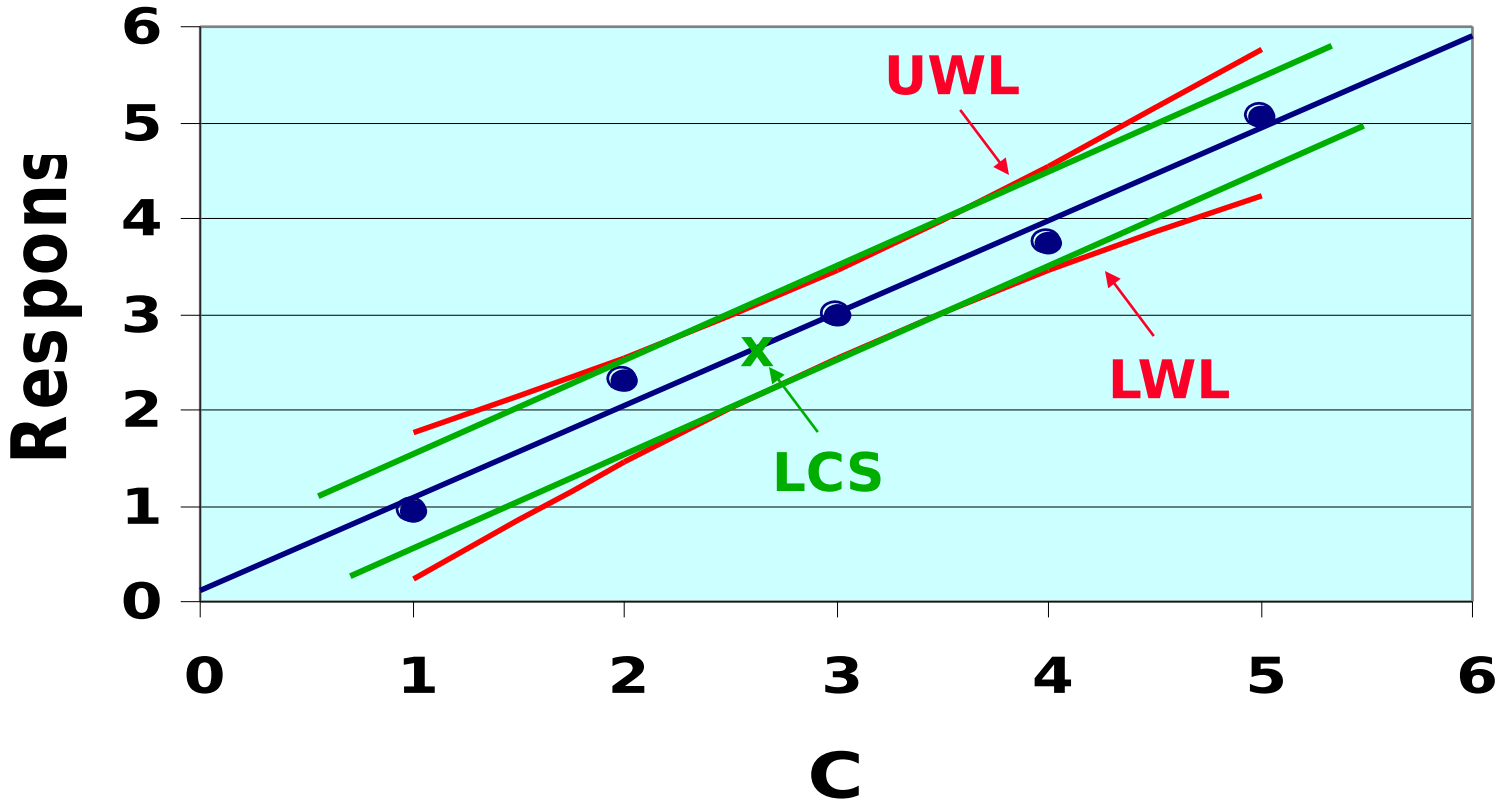


MQL Protocol

- MQL shall be reported and used with reliable precision and bias. MQL without precision and bias has no or limited use.
- Precision and bias of analytes with C $\geq$ MQL in a blank matrix would be similar to the LCS'.
- MQL $\geq 3 \times$ MDL

Accuracy of MQL Procedure

Mandel-Linnig Hyperbola



Assumption 1: Constant RSD at C ≥ MQL

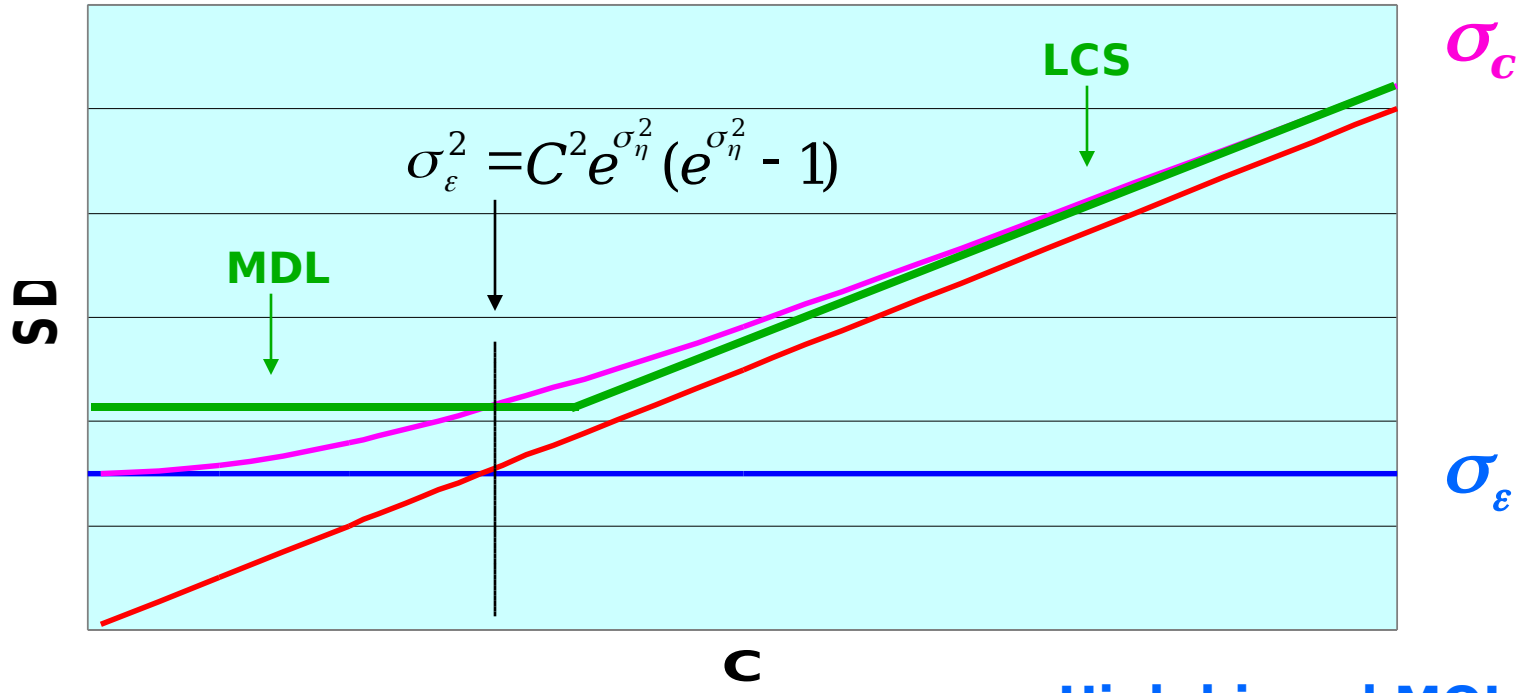
⇒ ⇒ ⇒ ⇒ ⇒ ⇒ ⇒ ⇒

High biased MQL with low biased uncertainty

Accuracy of MQL Procedure

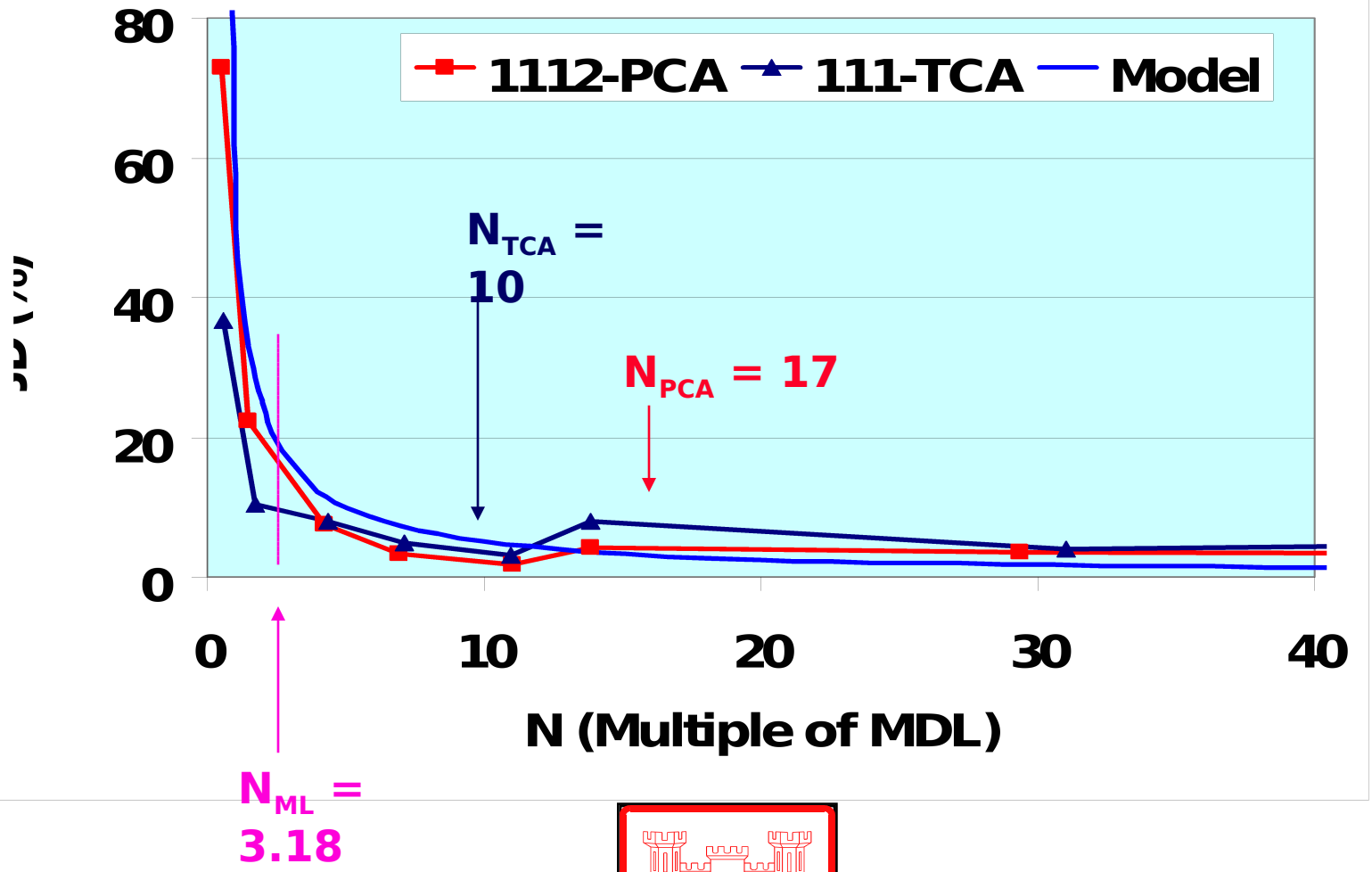
Rocke and Lorenzato Model

$$\sigma_C = \sqrt{\sigma_\varepsilon^2 + C^2 e^{\sigma_\eta^2}(e^{\sigma_\eta^2} - 1)} \approx \sqrt{2} \times \sigma_\varepsilon \quad for\ small\ C.$$



Assumption 2: Constant SD at C < MQL. ⇒ ⇒ ⇒ ⇒ ⇒ **High biased MQL with high biased uncertainty**

Accuracy of MQL Procedure



QC Issues

- MQL shall be verified on a routine basis
- MDL shall be properly determined
- LCS control limits shall be properly established
- $U_{95\%,\ MDL}$ may be replaced with $U_{95\%,\ MB}$

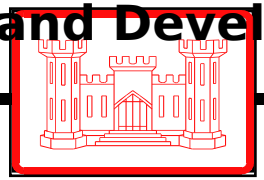
MQL vs. LCMRL

Method 521

Determination of Nitrosamines in Drinking Water by Solid Phase Extraction and Capillary Column Gas Chromatography with Large Volume Injection and Chemical Ionization Tandem Mass Spectrometry

Version 1.0, September, 2004
Document #: EPA/600/R-05/054

National Exposure Research Laboratory
Office of Research and Development, USEPA



MQL vs. LCMRL

Table 1. Detection Limits and Lowest Concentration Minimum Reporting Levels [a, b]

Analyte	DL (ng/L)	LCMRL (ng/L)
NDMA	0.28	1.6
NMEA	0.28	1.5
NDEA	0.26	2.1
NPYR	0.35	1.4
NDPA	0.32	1.2
NPIP	0.66	1.4

a. DLs determination from LFBs fortified at 1.0 ng/L (n = 8).

b. LCMRLs determined from LFBs fortified at 1.0, 2.0, 3.0, and 4.0 ng/L (n = 5 or 6 at each concentration).

MQL vs. LCMRL

Table 6. Precision and Accuracy Data Obtained from Fortified Reagent Water at Four Concentrations

Analyte	Fortified Conc 2.0 ng/L (n = 7)		Fortified Conc 4.0 ng/L (n = 6)		Fortified Conc 10.0 ng/L (n = 4)		Fortified Conc 20.0 ng/L (n = 6)	
	Accuracy (%R)	Precision (RSD)	Accuracy (%R)	Precision (RSD)	Accuracy (%R)	Precision (RSD)	Accuracy (%R)	Precision (RSD)
NDMA	94.7	12	92.7	11	88.7	3.8	89.5	7.8
NMEA	81.8	9.6	83.1	6.3	86.5	4.5	90.9	6.9
NDEA	84.6	9.0	92.0	14	87.5	9.1	95.6	11
NPYR	92.6	12	102	4.0	101	5.0	101	6.1
NDPA	81.7	8.0	87.6	7.3	97.0	10	87.1	7.7
NPIP	98.3	20	86.3	6.1	91.8	3.7	93.6	4.0

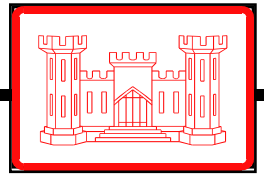
MQL vs. LCMRL

ANALYTE (Conc)	NDMA (2 ppt)	NDMA (4 ppt)	NDMA (10 ppt)	NDMA (20 ppt)	NDMA (pooled)
MATRIX	water	water	water	water	water
METHODS	3535/521	3535/521	3535/521	3535/521	3535/521
MDL (ppt)	0.28	0.28	0.28	0.28	0.28
LCS LCL (%)	131	126	100	113	113
LCS UCL (%)	59	60	77	66	71
MQL (ppt)	1.2	1.3	3.7	1.8	2.0
PRECISION (RSD)	12	11	4	8	7
BIAS (%R)	95	93	89	90	92

Method 521: LCRML = 1.6 ppt with %R = 50 - 150% @ 99% confidence.

Summary

- Simple, practical, and conservative procedure for estimating MQL.
- MQL is estimated based on in-house QC data.
- MDL and LCS studies shall be properly performed and documented.
- MQL shall be verified on a routine basis.
- MQL shall be reported with precision and bias.



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